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EXPERIMENTAL STUDIES ON THE CARDIOVASCULAR REFLEX FROM THE PERICARDIUM

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I. INTRODUCTION

It has been reported since about 1890 by various investigators such as Pianese, Michailow, Ruhemann, Tomaselli and Stöhr that specific sensory endings (the so-called Vater-Pacini's bodies) which may be assumed to be stretch-receptors are widely distributed over the pericardium of man. But the function these sensory endings discharge in the living body is not yet definitely clarified. It has hitherto been supposed that they may probably participate in the control of blood circulation through reception of pressure changes in the pericardial cavity due to the cardiac systole and diastole, but this supposition is not based on experimental data. Another widely current opinion is that the pericardium is simply a cardiac sac which affords a mechanical protection to the heart by relieving it of overburden, and thus secondarily restrains the rise of the pulmonary capillary pressure. At any rate, attempts to correlate the function of bodily organ to its morphology are full of difficulties, and more often than not lead to erroneous conclusions, but the present author is quite dissatisfied with the above traditional acceptance of the pericardium as a mere envelope without a vital function.

Leriche (1932) produced pericardial irritation in dogs by intrapericardial injec-

tion of isotonic saline, acid, or alkaline solutions, and thereby noted a remarkable fall of the systemic arterial pressure; and he tried to explain from this fact both the occurrence of shock in the case of pericardial trauma, and the fall of the systemic arterial pressure set off by brushing the pericardium during an intrathoracic operation. But he did not go further than direct public attention to this pericardial hypersensitivity.

Conception of the pericardium as a living organ should naturally lead to pursuit of the significance of this reflex physiology. Experimental and clinical recognition has already been given to the existence of prominant cardiovascular reflexes in such serous membranes as the peritoneum and pleura. But how about the pericardium, another serous membrane? This curiosity of the present author's was further stimulated by the following experimental and clinical facts.

II. MOTIVES OF THE PRESENT INVESTIGATION

Our laboratory has pursued researches on experimental constrictive pericarditis since 1953, and during the course of these researches KUMA, one of our associates, came across the following interesting fact. While he was taking measurements by catheterization of intracardiac pressures of dogs with experimental constrictive pericarditis, he happened to note in several cases with symptoms of right heart failure a sudden, two- or threefold rise of the right ventricular pressure which occurred without any exciting cause, and disappeared after a while. He supposed that this phenomenon might be due to heightened nervous reflexes from the diseased ventricular wall.

Shortly afterward the present author himself experienced the following interesting clinical case.

The patient was a boy aged 17. From the age of 10 he had complained of pain at the joints of his four extremities, and about the same time he suffered the onset of paroxysmal palpitation and dyspnea which especially bothered him in autumn. These symptoms having gradually become to serious, he had to be hospitalized in the Medical Clinic of our University Hospital. Auscultation revealed systolic murmurs at every valvular orifice, but no roentgenographic abnormalities were found in the size and shape of the heart. Electrocardiographic finding was normal. The mean value of the pulmonary capillary pressure, as measured by intracardiac catheterization, was 11.0 mm Hg, slightly higher than normal. The pulomnary artery showed a normal pressure, its systolic pressure being 22.2 mm Hg, its diastolic 10.0, and its mean value 16.0. The right atrial and ventricular pressures were also normal. The venous pressure fluctuated between 110 and 50 mm H_2O, thus showing marked daily variations. As Aschner's and Valsalva's tests, and sudden exposure to the cold wind brought on a fit of difficult breathing, the disease was considered due to some kind of disturbance of nervous reflexes. With a view to blocking the action of the vagus, three 50 mg tablets of Banthine and two 125 mg tablets of Begolysen were given daily for 20 days, but with no effects. And so thoracotomy was resorted to under the diagnosis of mitral stenosis.

On opening the thorax, the heart was found of normal size, but the entire pericardium was in a state of fibrinous adhesion. The adhesion, however, was of such a degree that it was possible to free the adherent membrane with fingers. Intracardiac pressures were measured by direct puncture. The pressure in the right atrium was 15 mm Hg, it recorded a normal type of pressure curve, and no murmurs were felt at the apex. As these findings almost completely ruled out mitral stenosis, the operation was limited to an extensive removal of the pericardium in the left side of the thorax, including the excision of the left phrenic nerve.

All of the preoperative complaints vanished after operation, and at present after elapse of three years he is at work in excellent health.

Such being the case, the adherent pericardium in this clinical case might have been so to speak, the trigger of the pathologic reflex, and so the cause of paroxysmal dyspnea.

The above two facts clinical and experimental have made the present author suspect the existence of the cardiovascular reflex from the pericardium, and aroused a desire in him to pursue its physiologic and pathologic significance.

III. METHODS

The normal or pathologic pericardia of 54 adult dogs weighing 8-15 kg were stimulated in various ways, and the effects of these stimulations on systemic arterial and venous pressures, on pulmonary arterial and right ventricular pressures, and on respiration and electrocardiographic findings were recorded.

The systemic arterial and venous pressures were measured by direct cannulization into the femoral artery and vein. The cannula was connected with either a mercury or water manometer, and pressures were recorded on a roll of soot paper with use of a kymographion. Respiration, too, was recorded on soot paper on a kymographion with the aid of a side tube attached to the intratracheal tube and connected with a rubber tambour. The pulmonary arterial and right ventricular pressures were measured by intracardiac catheterization or by direct puncture, and recorded, using an electromanometer.

The intravenous injection of Rabonal was used for anesthesia, and the experiments were done after respiration and the systemic arterial pressure had become stable in the experimental animals. During the course of thoracotomy artificial air respiration was practiced with use of an intratracheal tube.

IV. RESULTS

1. Electric Stimulation of the Normal Pericardium

(1) Rectangular-wave Electric Stimulations of the Normal Pericardium

Fig. 1 shows the changes in the femoral arterial pressure produced by rectangular-wave electric stimulations of the pericardium to various degrees. The pericardium being cut open, the stimuli were applied to its inside. The pericardial cavity was filled with liquid paraffin to prevent gliding of the current and insulate the epicardium. The electrode used for stimulation was of special construction; its

positive was made by curving the platinum wire into a circle with the diameter of 5 mm, and its dotlike negative was placed at the center of this circle.

As shown in the figure, stimulations with less than 15 volts were incapable of causing any change in the systemic arterial pressure, no matter how much frequency might be increased, but when currents of more than 15 volts were applied, arrhythmia and a marked fall of the systemic arterial pressure were noted. Continuation of stimulation for more than 2 minutes caused a whitish local burn, and application of electricity to this burnt site called forth no response any longer.

(2) Topospecificity of the Reflex for Stimulation

The pericardium was roughly divided into four parts, namely, right and left atrial and ventricular, and each of these parts was separately stimulated with rectangular-wave electric currents. But no definite and specific variations were thus produced in the systemic arterial pressure; that is, no topospecificity of the reflex was demonstrated, as shown in Fig. 2.

One case developed ventricular fibrillation after being stimulated in the left ventricular part of pericardium, but was saved from death by electroshock of the heart.

(3) Electric Stimulations of the Pericardium in the Case of Bilateral Cervial Section of the Vagi

Electric stimulations of the pericardium in the case of bilateral cervical section of the vagi, as shown in Fig. 3, produced no changes in respiration as well as in the systemic arterial and venous pressures.

(4) Summary of This Section

Rectangular-wave electric stimulation is most conveniently, and so frequently used in the studies of reflexes. But in the present investigation more than 15 volts were needed to awaken the pericardial cardiovascular reflex, and so it was impossible to stimulate the same site continuously for long. This technical difficulty is perhaps attributable to extreme tenuity of the cannine pericardium, and also to the very narrow space between the positive and negative of the electrode used. Moreover, in the case of pericardial adhesion this method cannot be used owing to the impossibility of insulating the epicardium. Therefore, if it is wished to draw comparison between the reflexes of normal and adherent pericardia, other methods of stimulation have to be employed.

2. Mechanical Stimulations of the Normal Pericardium

(1) Mechanical Stimulations of the Normal Pericardium

Arrhythmia and a marked fall of the systemic pressure are known to be causable by picking up the normal pericardium with a pincette, and giving it a strong pull, but this pull is not a purely pericardial stimulation, for the heart is also pulled with the pericardium. Therefore, if we wish to give a stimulus to the pericardium alone, some other methods have to be devided. In the present investigation a small section of the normal pericardium was selectively streched by intrapericardial injection in 2 cc volume of isotonic saline solution.

As shown in Fig. 4, respiration, electrocardiographic findings, and the systemic

arterial and venous pressures remained essentially unaffected by this method of stimulation.

(2) Injection of Isotonic Saline Solutionin to the Normal Pericardial Cavity

This time not a section, but the whole part of the pericardium was stretched by injecting into the pericardial cavity through a vinyl tube 50 cc of isotonic saline solution heated at 37°C. Results obtained by this method of producing artificial heart tamponade are presented in Fig. 5.

As shown in the figure, the above procedure caused a rapid fall of the systemic arterial pressure, and with it, bradycardia and slight increase the pulse pressure. But these latter two symptoms were soon replaced by the typical symptoms of heart tamponade, namely, tachycardia and a decrease of the pulse pressure. It is interesting to note that though the systemic arterial pressure rose to its former level on withdrawal of the injected saline solution, it again fell remarkably, and bradycardia, too, reappeared after a while.

(3) Injection of Air into the Rubber Bag Fixed in the Normal Pericardial Cavity

Pericardial stretching without the simultaneous occurrence of heart tamponade was aimed at in this experiment. Results obtained are presented in Fig. 6.

A rubber bag was put into the pericardial cavity, and on its cardiac side was a piece of cardboard placed. The cardboard and pericardium thus holding the bag between them, the former was fixed to the latter by suture. The air was pumped into the bag from the outside. When the tension rose to 50 mm Hg in the bag, the typical symptoms of heart tamponade appeared; that is, the systemic arterial pressure fell remarkably, and the venous pressure showed rise. But when the tension stood at 23 mm Hg, the venous pressure showed no rise, and were noted marked bradycardia, depressed systemic arterial increased pulse and slightly depressed pulmonary arterial pressures.

(4) Selective Stretching of the Normal Pericardium

This experimient was devised further to reduce the effects of pericardial stretching upon the heart. As shown in Fig. 7, a long, lengthwise incision was made along the middle line of the membrane, which was then freed from the heart. Two strings were tied to each of the right and left edges of the wound, and then passed out of the body through their respective sides of the thorax. After closing the thorax, pericardial stretching was achieved by pulling the strings from both sides. As shown in the figure, the systemic arterial pressure and electrocardiographic findings remained the same.

The figure on the right shows results of this experiment on a dog with bilateral cervial section of the vagi. As shown in this figure, the systemic arterial pressure suffered no change. In another dog the electromanometric recording of changes in the systemic arterial pressure was conducted simultaneously with electrocardiography. The results are given in Fig. 8. As shown in the figure, the systemic arterial pressure fell by 70 mm Hg. Fig. 9 shows results of the above experiment on a dog with bilateral section of the vagi. As shown in the figure, the systemic arterial

pressure remained unaffected in this case.

(5) Summary of This Section

Leriche (1932) noted a marked fall of the systemic arterial pressure in dogs when he injected 2 cc of isotonic saline solution into the normal pericardium. But in the present investigation such a selective partial stretching of the pericardium awakened no appreciable response. Selective stretching of a large or the whole part of the membrane, however, was always accompanied by depression of the systemic and pulmonary arterial pessures. It is therefore considered that the cardiovascular reflex first makes its appearance when the internal tension brought to bear upon the pericardium has crossed a certain threshold.

Murata and Eguchi (1952) induced artificial heart tamponade in rabbits by injecting blood or isotonic saline solution into the pericardial cavity, and investigated the effects of the thus increased intrapericardial tension upon the systemic arterial and venous pressures, and electrocardiographic findings. They reported that there was a nearly parallel relation between the cervical arterial pressure and the intrapericardial tension, and that when the intrapericardial tension became higher than the femoral venous pressure, the pressure in the cervical artery fell remarkably. Considering from results of the present investigation, it seems that these authors did not notice the appearance of the cardiovascular reflex due to pericardial stretching, which must have preceded the typical symptoms of heart tamponade. As shown in Fig. 5 and 6, the intracardial tension too low for the development of heart tamponade caused a depression of the systemic arterial pressure, bradycardia, and an increase of the pulse pressure. Further, as shown in Fig. 6, a selective pull of the pericardium caused decrease in the arterial pressures, pulmonary as well as systemic, and so it seems that the pulmonary arterial pressure reflexly falls together with the systemic when overloading of the ventricles reaches a certain limit, and extends the pericardium. Such being the case, this reflex may be regarded as one of the factors responsible for the nervous control of the pulmonary circulation, of which a detailed mention will be given later.

This cardiovascular reflex due to mechanical stimulation of the pericardium vanishes in the dog with bilateral cervical section of the vagi, as was also noted in the case of electric stimulation. It is therefore probable that this reflex runs in the main stems of vagi.

3. Chemical Stimulations of the Normal Pericardium

(1) Subepicardial Injection of Acetylcholine

1.0 cc of 0.005% acetylcholine solution was injected into the subepicardium. As shown in Fig. 10(a), the systemic arterial pressure temporarily fell, but as the drug was absorbed, bradycardia and increase of the pulse pressure gradually became prominant.

(2) Intrapericardial Injection of Epirenamine Hydrochloride

1.0 cc of 0.1% solution of epirenamine hydrochloride was injected into the pericardium. As shown in Fig. 10(b), the systemic arterial pressure began gradually to rise 40 seconds after injection, reached the highest level 110 seconds later, and

maintained it afterward. This phenomenon is purely the effect of drug absorption, and cannot be regarded as due to the reflex.

(3) Stimulation with Acetylcholine of the Inside of the Normal Pericardium

A piece of gauze 3 × 3cm in size was soaked in 0.005% acetylcholine solution, and then applied to the inside of the normal pericardium. As shown in Fig. 11, bradycardia, increase of the pulse pressure, and remarkable fall of the systemic arterial pressure were noted immediately after application. The venous pressure was also raised. With withdrawal of the gauze the systemic arterial Pressure began to rise, and the venous pressure gradually to fall.

(4) Injection of Acetylcholine into the Normal Pericardial Cavity

2.0 cc of 0.005% acetylcholine solution was injected through a fine vinyl tube into the normal pericardial cavity. As shown in Fig. 12 (a, b), immediate fall of the systemic arterial pressure, bradycardia and increase of the pulse pressure were noted, as in the above case. The venous pressure and electrocardiographic findings showed no change. By the way, in this case given in the figure, depression of the pulmonary arterial pressure was extremely slight, but moderate in many other cases. Following the above injection, 1 cc of a solution of atropine sulphate was injected into the pericardial cavity after the same fashion. As shown in (b), the systemic pressure gradually rose after this injection, and soon regained its former level.

(5) Injection of Acetylcholine into the Pericardial Cavity in the Case of Unilateral Cervical Section of the Vagus

As shown in Fig. 13 (a, b), with right unilateral cervical section of the vagus the systemic arterial and venous pressures commenced a rise, and also electrocardiographically the depression of ST-segment and inversion of T-wave were noted. 2.0cc of 0.005% acetylcholine solution was now injected into the pericardial cavity. This injection caused respiratory acceleration, and a marked fall of the systemic arterial pressure, but when the left cervical branch of the vagus was also severed 2 minutes later, the systemic arterial pressure again began to rise, and respiration, too, slowed down. The abnormalities of ST-segment and T-wave were also normalized.

(6) Injection of Acetylcholine into the Pericardial Cavity in the Case of Bilateral Cervical Section of the Vagi

2 cc of 0.005% acetylcholine solution was injected into the pericardial cavity of the dog with bilateral cervical section of the vagi. As shown in Fig. 14, the systemic arterial pressure drew a gentle downward curve observable in the case of acetylcholine absorption. The venous pressure remained unaffected.

(7) Investigation with P^{32} of Absorption of Acetylcholine Injected into the Pericardial Cavity

200 μc of P^{32} in the form of sodium phosphate was dissolved in 1 cc of isotonic saline solution, and injected into the pericardial cavity together with 2 cc of 0.005% acetylcholine solution. Every 10 seconds after injection blood was taken from the femoral artery, and the amount of P^{32} contained in it was measured with a Geiger counter. Normal blood counted 52. Ten seconds after injection the count increased by 30, but hardly till 30 seconds later. Really remarkable increase of the count was

witnessed 40 seconds later. On the other hand, the systemic arterial pressure began to fall within 10 seconds after injection, reached its lowest level in 15 seconds, and 30 seconds later showed a slight upward tendency. The pulmonary arterial pressure, too, began to fall immediately after injection, and was at its lowest level 2 seconds later.

(8) Summary of This Section

As already stated in the section on "Mechanical Stimulations", stimulation of the whole pericardium is necessary for the appearance of the pericardial cardiovascular reflex, and this holds true also in the case of chemical stimulations.

LERICHE (1932) noted that the intrapericardial injections of acid and alkaline solutions exerted by far more powerful depressing influence on the systemic arterial pressure than those of isotonic saline solution, and warned against the use of the Dakin' solution for irrigation of the pericardial cavity, which was then in vogue in the treatment of suppurative pericarditis; he feard that it might provoke a shock of pericardial origin. In this case of Leriche, however, stimulations with acid and alkaline solutions were limited to a small part of the pericardium.

Application of acetylcholine to a part of the pericardium produced nearly the same results as the injection of the same drug into the pericardial cavity, and so in the present investigation the latter method was adopted for stimulation of the whole pericardium. With this method, however, it is impossible to prevent the spread of stimulation to the epicardium, but as shown in Fig. 10 (a), the epicardial response to the injection was not a reflex, but clearly an effect of drug absorption.

Another knotty problem in chemical stimulations is to distinguish a pure reflex action from the effects of drug absorption. In the case of the intrapericardial injection of epirenamine hydrochloride the systemic arterial pressure rose 40 seconds after injection, as shown in Fig. 10 (b), and again, as shown in Fig. 15, remarkably high Geiger counts of peripheral blood, and stabilization of the systemic arterial pressure were obtained 40 seconds after combined injection of P^{32} and acetylcholine into the pericardial cavity. On the other hand, fall of the systemic and pulmonary arterial pressures occurred respectively within 10 and 2 seconds after injection of acetylcholine into the pericardial cavity. Therefore, it cannot but be considered that this pressure depression occurred, not as an effect of drug absorption, but purely reflexly.

MURATA and EGUCHI (1952) also investigated the absorptive power of the pericardium with use of P^{32}, and reported that if injected into the pericardial cavity, P^{32} appeared in the peripheral arterial blood 1-5 minutes later, and in the urine 4-11 minutes later. But in the present investigation it has been proved that absorption of P^{32}, though in a very small amount, commences within 10 seconds after injection. By the way, REHN (1913) noted the appearance of indigocarmine in urine within 5 minutes after injection of its solution into the pericardial cavity.

With regard to the actions of acetylcholine on the pulmonary artery and vein, there are many papers dealing with them. HARRIS (1957), experimenting with clinical cases, directly injectied acetylcholine into the pulmonary artery, and in about

one-third of total cases he noted a fall of the pulmonary arterial pressure and rise of the wedge pressure, but no changes in the systemic arterial pressure. In the other two-thirds, he observed, the pulmonary arterial pressure remained unaffected. Wood, Besterman et al. (1957) likewise injected acetylcholine into the pulmonary arteries of patients with mitral stenosis in volumes not large enough to affect the systemic arterial pressure, and noted a fall of the pulmonary arterial pressure, and rise of the wedge pressure. Also Nuki (1954) stated that acetylcholine exerted a depressing influence upon the pulmonary circulation by constricting the pulmonary venules, but leaving the arterioles unaffected. In the present investigation the injection of the said drug indeed caused a depression of the pulmonary arterial pressure, but this depression occured within 2 seconds after injection, and moreover, preceded the depression of the systemic arterial pressure. Therefore, this phenomenon can neither be ascribed to the action of the absorbed acetylcholine on the blood-vessels of the lungs, nor regarded as a result of depression of the systemic arterial pressure. The only alternative left is to think that it occurred reflexly as a result of pericardial irritation caused by the said drug.

4. Chemical Stimulations of the Adherent Pericardium

A variety of pathologic conditions were produced in the pericardium to know what kind of cardiovascular reflex would come from the diseased membrane.

Partial pericardial adhesion was made by rubbing a part of the pericardium violently with a piece of gauze; whole pericardial adhesion by injecting into the pericardial cavity 1 cc of tincture of iodine; and constrictive pericardial adhesion by inserting a polyvinylformal sponge into the cavity.

As stated above, it is impossible to stimulate the adherent pericardium mechanically or with electricity, and so the injection of acetylcholine into the pericardial cavity was used as a method of stimulation in these experiments on diseased pericardia. The results thus obtained were compared with those of the experiments on normal pericardia.

(1) Stimulation with Acetylcholine of the Partially adherent Pericardium (10 Days after Production of Adhesion)

Ten days after production of partial pericardial adhesion 2 cc of 0.005% acetylcholine solution was injected into the pericardial cavity of the dog. As shown in Fig. 16, the systemic arterial pressure immediately and violently fell by 80 mm Hg, and breathing, too, became faster and deeper. The venous pressure rose three times as high as its former level, and also electrocardiographically the inversion of T and lowering of Ta became very noticeable. As to the pulmonary arterial pressure, its systolic pressure rose from 18 to 30-38 mm Hg, and its diastolic from 3 to 10mm Hg. These reactions, however, were completely counteracted by injecting 1 cc of a solution of atropine sulphate into the pericardial cavity.

(2) Stimulation with Acetylcholine of the Wholly Adherent Pericardium (1 Month after Production of Adhesion)

The wholly adherent pericardium was partially liberated 1 month after pro-

duction of adhesion, and acetylcholine was injected into the thus made pericardial cavity. As shown in Fig. 17, after injection were noted, as in the above experiment, the depression of the systemic arterial pressure amounting to 60 mm Hg, respiratory acceleration, nearly twofold increase of the venous pressure, and electrocardiographically lowering of Ta, and flattening of T. The systolic pressure of the pulmonary artery rose from 30 to 38 mm Hg, and the diastolic from 3 to 8 mm Hg.

(3) Stimulation with Acetylcholine of the Constrictive Adherent Pericardium (2 Months after Production of Constrictive Adhesion)

Results of this experiment are given in Fig. 18. As shown in the figure, the systemic arterial pressure showed the mild depression amounting to 40 mm Hg, and the venous pressure which had already been 60 mm H_2O before stimulation remained unaffected. Electrocardiographically the marked inversion of T-waves was noted. As to the right ventricle, its systolic pressure rose from 25 to 35 mm Hg, and its diastolic from 0 to 2 mm Hg.

(4) Effects of Stimulation with Acetylcholine on Long-standing Pericardial Adhesion (16 Months after Production of Adhesion)

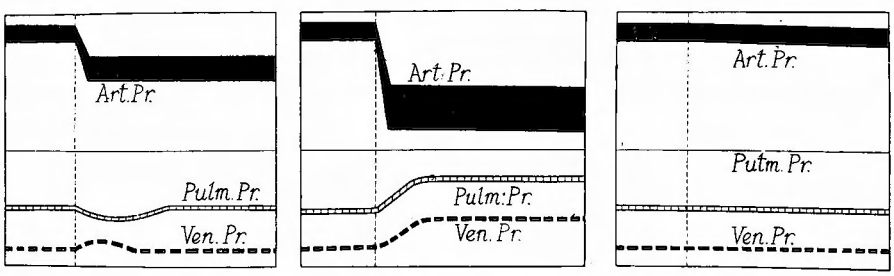
A case of whole pericardial adhesion was likewise stimulated with acetylcholine 16 months after production of adhesion. As shown in Fig. 19, the systemic arterial pressure showed a slow depression which might be attributed to the action of the absorbed drug. The pulmonary arterial pressure, too, fell very slowly. The cardiovascular reflex was not recognized in this case.

(5) Summary of This Section

As will be seen from what has been stated above, the adherent pericardium, if stimulated, reflexly produce quite different symptoms from those noticed on stimulation of the normal pericardium, namely, pathologically hypersensitive depression of the systemic arterial pressure, two- or threefold elevation of the venous pressure, flattening or inversion of T-waves, lowering of Ta, and 30-70% elevation of the pulmonary arterial pressure.

As shown in the schema, these pathologically hypersensitive reflex symptoms are especially conspicuous in those cases of recently-produced and still inflammatory pericardial adhesion, and the degree of reflex hypersensitivity seems to have nothing to do with the degree and extent of adhesion. It should be noted that the pericardium completely cicatrized owing to long-standing adhesion gives no reflex symptoms any longer.

General View of Pericardial Depressor Reflex



A: Normal Pericardium B: Inflammatory Adherent Pericardium C: Longstanding Adherent Pericardium

Stimulation with Ach of the Pericardium		Normal Pericardium	Inflammatory Adhesive Pericardium	Longstanding Adhesive Pericardium
Fall of the Systemic Arterial Pressure		+	++～+++	−
Increase of the Pulse Pressure		+	++～+++	−
Bradycardia		+	++～+++	−
Reise of the Venous Pressure		−～+	+～++	−
Pulmonary Arterial Pressure	Reise of the Systolic Pr.	−	+++	−
	Reise of the Diastolic Pr.	−	++	−
	Fluctuation with the Respiration	+	++	−
Acceleration of the Respiration		+	+++	−
ECG	Inversion of the T-wave	−	+～++	−
	Depression of the ST-segment	−	+	−

5. Cardiovascular Reflexes from the Peritoneum and Pleura

Again with use of acetylcholine the peritoneum and pleura were stimulated to ascertain what kinds of cardiovascular reflexes these serous membranes were in possession of. The results obtained were compared with those of the above experiments.

(1) Injection of Acetylcholine into the Normal Peritoneal Cavity

2 cc of 0.005% acetylcholine solution was injected into the normal peritoneal cavity. As shown in Fig. 20 (a, b), extrasystolic arrhythmia appeared immediately after injection. A mild rise of the systemic arterial pressure was also observed, but this pressure showed a slight fall about 50 seconds later. The venous pressure began to rise 70 seconds later. No respiratory changes occurred. The systemic arterial pressure returned to its former level 5 minutes after injection.

(2) Injection of Acetylcholine into the Normal Pleural Cavity.

2.0 cc of 0.005% acetylcholine solution was injected into the normal pleural cavity. As shown in Fig. 21, the systemic arterial pressure began to fall immediately after injection, and reached its lowest level 20 seconds later. After then it showed a temporary upward tendency, but with recommencement of its fall 60 seconds after injection bradycardia and increase of the pulse pressure also came. No marked post-injection variations were noted in the venous pressure and electrocardiographic findings. Breathing became faster simultaneously with the injection. The pulmonary arterial pressure showed a mild depression.

(3) Injection of Acetylcholine into the Adherent Pleural Cavity

Partial pleural adhesion was produced by rubbing, and 2 weeks later acetylcholine was injected into the pleural cavity. As shown in Fig. 22, the systemic arterial pressure was not so sensitively affected as in the case of stimulation of the normal pleura; it did not begin to fall slowly till about 20 seconds after injection. As for the venous pressure, it began to rise just after injection, and ultimately reached

nearly two times as high as its preinjection level. The depression of ST-segment, and flattening of T-wave were electrocardiographically observed 25 seconds after injection. Rise of the pulmonary pressure commenced 30 seconds after injection, and its systolic pressure showed 5% elevation 70 seconds later.

(4) Summary of This Section

Many papers have already been written on the cardiovascular reflexes from the peritoneum and pleura. Hess and Wyss (1922) stated that the mesenterium was in possession of specific receptors for mechanical stimulation concerned with the cardiovascular reflex. As to the peritoneum, Goltz's experiment (Klopfversuch) is widely known. Nakamura (1938) also noted the occurrence of bradycardia and depression of the systemic arterial pressure when he stimulated the parietal peritoneum and the mesenterium with warm water heated at 50°C. As to the gastrointestinal tract, stimulation with acetylcholine caused its constriction, but as shown in Fig. 20, the systemic arterial pressure showed an upward tendency. With gradual absorption of acetylcholine, however, the depressing influence of the drug upon the cardiovascular system came to make itself felt; hence depression of the systemic arterial pressure and bradycardia. Stimulation with the same drug of the peritoneum caused no respiratory changes. With regard to the normal pleura, its stimulation with acetylcholine brought on the peculiar biphasic depression of the systemic arterial depression, as shown in Fig. 21. The first phase was characterized by tachycardia, and the second by bradycardia. Respitatory acceleration was more remarkable than in the case of stimulation of the pericardium. As for the pulmonary arterial pressure, it made diverse responses to the injection of acetylcholine; in some cases it showed a depression, but in others no change. In the case of injection of the said drug into the adherant pleural cavity the pulmonary arterial pressure did not behave in a definite manner; in some cases it showed a mild rise, while in others it remained unaffected. But in fresh cases of pleural adhesion with residual inflammation the pulmonary arterial pressure as a rule took a mild upward tendency. It may be supposed from this that the whole pulmonary vascular system is in a state of heightened resistance when pleural inflammation is present.

On the cardiovascular reflex from the pleura there are already many clinical reports which deal, among others, with pleural shock in cases of pneumothorax, the vagovagal reflex often noted during an intrathoracic operation, and the effects of adrenal cortical hormones on the pleural reflex (Bergmann and Karlhuber, 1957). Takino (1950) asserted that the pleural cardiovascular reflex took its origin, not in the visceral pleura, but in the parietal, and supposed that its afferent route might pass in the pain nerve. But as shown in Fig. 21, the cardiovascular reflex was still present in the sufficiently anesthtized cannine pleura quite insensitive to pain. And so it is very problematical to regard the pain nerve as its sole afferent route.

Capps and Coleman (1932) made an extensive study on the sensibilities of the human pleura, percairdium and peritoneum, and stated that the upper serous part of the human pericardium was lacking in pain sense, but the lower fibrous part (below the 5th or 6th intercostal space) was sensitive to pain, being supplied by

afferents from the phrenic nerve. But no topospecificity of the pericardial cardiovascular reflexes from the pleura and peritoneum are quite different in action and aspect from that from the pericardium. Even in the case of stimulation of the diseased pleura no single instance of marked rise of the pulmonary arterial pressure was obtained. This fact alone is an ample evidence of the specificity of the pericardial cardiovascular reflex.

V. DISCUSSION

1. Cardiovascular Reflexes from the Heart and Its Vicinity

A comprehensive survey of studies on the cardiovascular reflexes from the heart and its vicinity was published by AVIADO and SCHMITT (1955). V. BEZOLD and HIRT (1867) caused depression of the systemic arterial pressure, bradycardia and respiratory standstill by intravenous injection of veratrin alkaloids, especially veratridin. And they stated that these symptoms were reflexly provoked by stimulation of the afferent nerve endings in the heart, and that these afferents passed through in the vagus. Though CRAMER (1915) and BRODIE (1900) asserted that the receptors concerned with this reflex were pressent in the lungs, JARISCH and RICHTER's experiment (1937) proved beyond doubt that the heart itself possessed these receptors, as BEZOLD had originally believed. At present the so-called BEZOLD-JARISCH's reflex means bradycardia and depression of the systemic arterial pressure which are caused by injecting any chemical substance into the coronary circulation. FUKUDA (1937) caused this reflex by using cardiotonics such as digitalis and adrenalin, while IKEDA (1957) noted that mechanical dilatation of the coronary vessels produced depression of the systemic arterial pressure. The latter also discovered the nerve endings at the root of the coronary artery which looked like pressoreceptors. The relation between these receptors and the chemoreceptors in BEZOLD-JARISCH's reflex is not yet ascertained.

SCHWIEGK, CHURCHILL and COPE (1935) reported that the artificially induced elevation of the pulmonary arterial pressure led to bradycardia and depression of the systemic arterial pressure. This reflex is now called SCHWIEGK's reflex or Lungenentlastungsreflex (W. R. HESS). This reflex is shared also by the pulmonary vein, and TAKINO (1937) and NONIDEZ (1937) were able to demonstrate in the wall of the pulmonary vein the presence of the sensory nerve endings which might be taken as pressoreceptors. As we have just seen, many papers have been written on the cardiovascular reflexes from the heart and its vicinity, but we have not yet a single report on the cardiovascular reflex from the pericardium.

2. Significance of the Normal Pericardial Depressor Reflex

The pericardium has hitherto been regarded as a mere cardiac sac which mechanically prevents overdilatation of the left ventricle, and secondarily restrains elevation of the pulmonary capillary pressure. This mechanical role has been reported by many investigators. KUNO (1915), by stretching the pericardium, measured the maximum pressure it could tolerate, and noted that its removal induced increased ventricular work and blood volume. HENDERSON (1914), FINEBERG (1936) and

WILSON (1937) demonstrated that pericardial capacity was larger than that of the normal heart at the time of its diastolic filling. NELEMANS (1940), BERGLUND (1952, 1955) and ISAACS (1954, 1955) experimantally proved that owing to the presence of the pericardium overdilatation of the left ventricle interfered with that of the right ventricle, and thus reduced the stroke volume of the latter with a result of maintaining at low levels both the pulmonary arterial pressure, and the amount of blood in the pulmonary circulation.

The pulmonary circulation which differs on several characteristic points from the systemic has also been treated in many papers. COURNAND et al. (1947) stated something to the following effect: "The difference between the pulmonary arterial and capillary pressures is about 6 mm Hg, and so about one-tenth of the difference between the mean systemic arterial and peripheral capillary pressures. As the amount of blood in the systemic and pulmonary circulations are nearly the same, the pulmonary circulation, compared with the systemic, meets less resistance from the arterioles. Accordingly the distribution of blood in the pulmonary circulation is largely influenced, not by nervous control, but by local mechanical conditions". This view of Cournand et al. finds much approval at present. But on the other hand there are many investigators who attach high importance to the nervous control of the pulmonary circulation. EULER and LILJESTRAND (1946), and LILJESTRAND (1948) noted in their experiments with cats that anoxia brought about the rise of the pulmonary arterial pressure without affecting the left ventricular pressure, and concluded that this phenomenon was due to the nervous or humoral constriction of the pulmonary vessels. NISELL (1951) asserted that anoxia and excessive CO_2 tension constricted the pulmonary veins and venules, but dilated the arteries and arterioles. HARRIS (1957), as mentioned above, by injection of acetylcholine into the human pulmonary artery, caused the fall of the pulmonary arterial pressure which was unattended with the concomittant fall of the systemic arterial pressure, and pointed out the possibility of nervous control of the pulmonary circulation. SARNOFF (1952) noted in rabbits the rise of the pulmonary arterial pressure after intracisternal injection of fibrin, and discussed the neurohemodynamics of pulmonary edema. The importance of the nervous control of the pulmonary arterial pressure in diseased conditions was emphasized by various authors: by HALMAGIE et al. (1953) in cases of heart failure; by TEMESVÁRÉ et al. (1957) in cases of patency of the ductus botalli; and by WOOD et al. (1956) in cases of mitral stenosis.

The present author experimentally demonstrated that concomittant fall of the systemic and pulmonary arterial pressures was causable by stimulating the normal pericardium. The knowledge of this pericardial reflex is indispensable for understanding both the physiologic functions of this membrane and physiology of pulmonary circulation. The pericardium, as stated above, is not a mere dead envelope; its depressor reflex pretects the pulmonary vascular bed, and prevents pulmonary hypertension.

It is well-known that the aortic arc and carotid sinus are in possession of depressor reflexes which respond to any elevation of the pressure of blood. These

reflexes are a part of the bodily mechanism which maintains the unity of internal conditions in dynamic balance, and which CANNON called homeostasis. The pericardial depressor reflex demonstrated in the present investigation may be considered as one of the homeostatic reflexes.

This pericardial reflex desappears with bilateral cervical section of the vagi, but the nervous connection between the pericardium and the pulmonary artery is still very obscure. Anatomically the surface of the pericardium is very intimately related with the pulmonary vascular bed through the superficial cardiac nerve plexus, but it is not clear whether or not the depressor reflex travels in this plexus. But as this plexus passes the hilum, and along the bronchus into the lung, it is highly probable that this pericardial reflex has something to do with the fall of the systemic arterial pressure often noted during an operation on the hilum.

3. Significance of the Pathologic Pericardial Reflex

When once the pericardium becomes diseased, the above-mentioned dynamic balance is lost; that is, in fresh cases of still inflammatory pericardial adhesion stimulation of the pericardium produces violent depression of the systemic arterial pressure, two- or threefold rise of the venous pressure, and more important, sudden, nearly twofold rise of the pulmonary arterial pressure. This condition is just the reverse of SCHWIEGK's reflex, and a result of enormous strain imposed on the living body by the stimulation. As a matter of fact, insufficiently anesthetized dogs screamed and wriggled with pained looks during the process of stimulation, and the clinical case mentioned at the beginning of this paper might probably have often been tortured by such a terrible fit. It has hitherto been said that all cases of simple adherent pericarditis passes on without any symptoms, but this does not seem to be the case. It may safely be assumed that many cases of adherent pericarditis are included among those carelessly diagnosed as neurocirculatory asthenia because of their unknown etiology. On the other hand it has been shown in the present investigation that no reflex comes from the completely cicatrized pericardium; that is, pericardial adhesion itself is not a sufficient condition of the pathologic reflex, and what matters is whether the membrane possesses pathologic hypersensitivity or not. From this an inference may be drawn that the clinical case mentioned at the beginning, if amply treated with antiphlogistics such as cortisone and ACTH, might have been completely cured before surgical intervention.

Our next problem is to probe into the causative mechanism of the elevation of the pulmonary arterial pressures due to stimulation of the pathologic pericardium.

The pulmonary vascular bed is originally very elastic, and generally keeps pressure fluctuations within certain bounds, and so in a normal individual the pulmonary arterial pressure is not so easily affected as the systemic by an increase of the blood volume in the pulmonary circulation. But according to EULER and LILJESTRAND (1946) the pulmonary vascular bed loses in elasticity in anoxia and chronic cases of pulmonary diseases, and so in such cases the pulmonary arterial pressure is apt to rise on the least provocation. SCHÄFER (1952), too, stated that anoxia brought on vagotonia. Also in the present investigation it has been noted that the patholo-

gic pericardial depressor reflex becomes more prominant in dogs in a state of anoxia. Therefore, it may safely be inferred that the appearance of the pathologic reflex is due to considerable impairment of elasticity of the pulmonary vascular bed in dogs with diseased pericardia.

YOSHIHARA et al. (1958) noted that acute pulmonary edema occurred in 88% of experimental dogs, when the pulmonary arterial pressure were raised to 40 mm Hg, and in 50%, when it was raised to 30 mm Hg. In the present investigation the pulmonary arterial pressure rose to 30-40 mm Hg in all experimental cases, and in addition to this, the systemic arterial pressure fell remarkably. This was the condition most suitable for the development of acute pulmonary edema. It is therefore considered that this pathologic pericardial depressor reflex has a great surgical significance.

VI. CONCLUSIONS

(1) With use of dogs the present author confirmed the existence of the pericardial cardiovascular reflex.

(2) This reflex has no topospecificity, and is caused by stimulating the whole pericardium.

(3) Adequate stimuli for this reflex are provided by stretching. In the case of stimulation of the normal pericardium the fall of the pulmonary arterial pressure always occurs simultaneously with that of the systemic arterial pressure. This reflex, as one of the homeostatic reflexes, keeps the heart from being overloaded, and at the same time protects the pulmonary vascular bed.

(4) But the reflex from the diseased pericardium is very hypersensitive, and assumes a pathologic nature. It causes a violent fall of the systemic arterial pressure, and nearly twofold rise of the pulmonary arterial pressure, and thus imposes such an enormous strain upon the individual that it provokes an intense paroxysmal dyspnea, and provides an etiologic condition for acute pulmonary edema.

(5) Both the normal and pathologic pericardial depressor reflexes vanish, when inflammation has gone from, and cicatrization has been completed in the adherent pericardium.

(6) The cervical bilateral branches of the vagus seem to participate in the transmission of this reflex.

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和文抄録

心膜から起る心臓血管反射に関する実験的研究

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河　端　修　一

著者は，単なる癒着性心膜炎の患者の，癒着心膜を剝離切除しただけで術前の激しい呼吸困難発作が全く消失した1臨床例，及び，実験的収縮性心膜炎の犬の心内圧測定中に，屢々原因不明の一過性の肺動脈圧亢進を認める事実等より，病的心膜が起点となつておこる心臓血管反射が存在するのではないかとの疑問を抱いて実験に着手し，次の事実を証明した．

(1)　成熟犬を用いて，心膜からおこる心臓血管反射の存在を確認した．

(2)　本反射は部位特異性を示さず，心膜全体からおこる心臓血管反射である．

(3)　本反射の適刺戟は，伸展刺戟であり，正常心膜に伸展を加えると，体動脈圧の下降と共に肺動脈の下降が認められる．即ち，心臓に過負荷がおこつた場合，心膜も共に伸展されて，肺動脈圧が反射的に下降し，抵抗の弱い肺血管床が保護されている一種の Homeostatic Reflex と思われる．

(4)　しかし心膜が病的になつている場合には，本反射も非常に病的となり，刺戟が加わると，体動脈圧は急激な下降を示し，逆に肺動脈圧は2倍近くの上昇を示す．このような状態は，生体にとつて非常な負担であり，激しい呼吸困難発作も招来するであろうし，又，急性肺水腫の原因にもなりうる．

(5)　以上の反射は，既に炎症が消退して瘢痕化した癒着心膜からはもうおこらなくなる．

(6)　本反射は，両側迷走神経の頸部切断犬では認められなくなるので，その経路は両側迷走神経主幹内にあるものと考えられる．

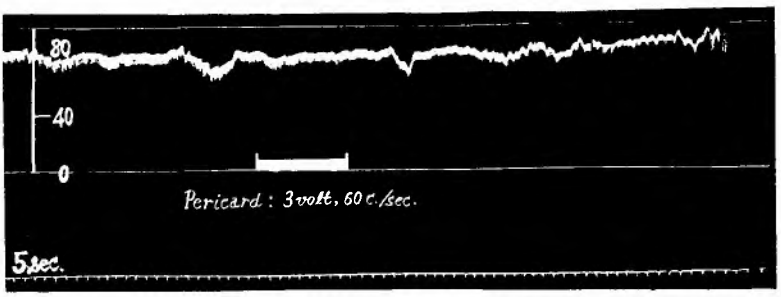
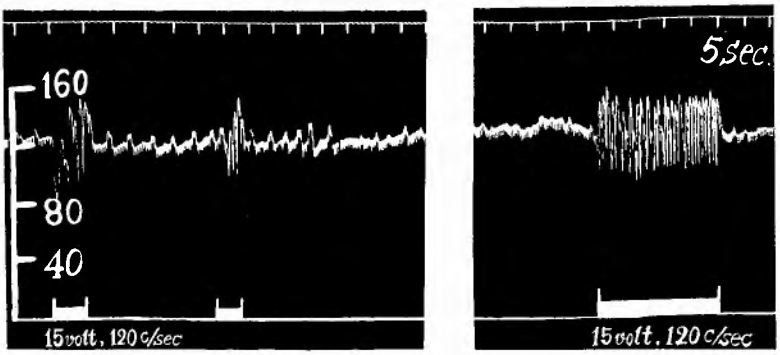


Fig. 1. Rectangular-wave electric stimulations of the normal pericardium.



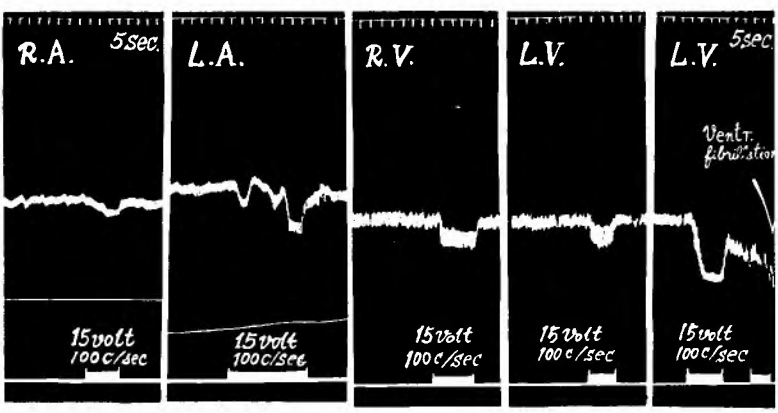


Fig. 2. Topospecificity of the reflex for stimulation.

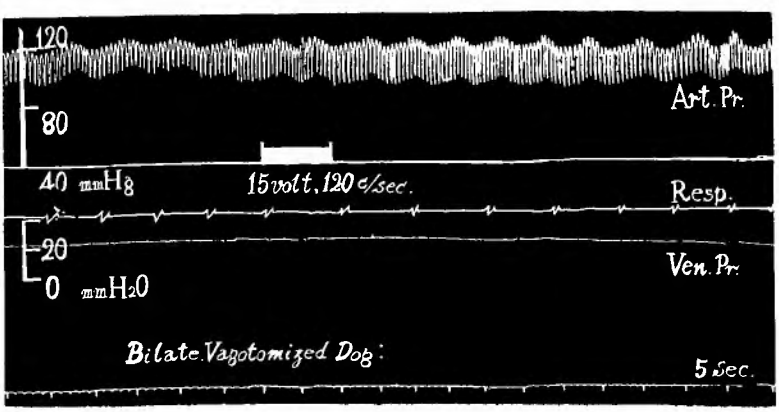


Fig. 3. Electric stimulation of the pericardium in the case of bilateral cervical section of the vagi.

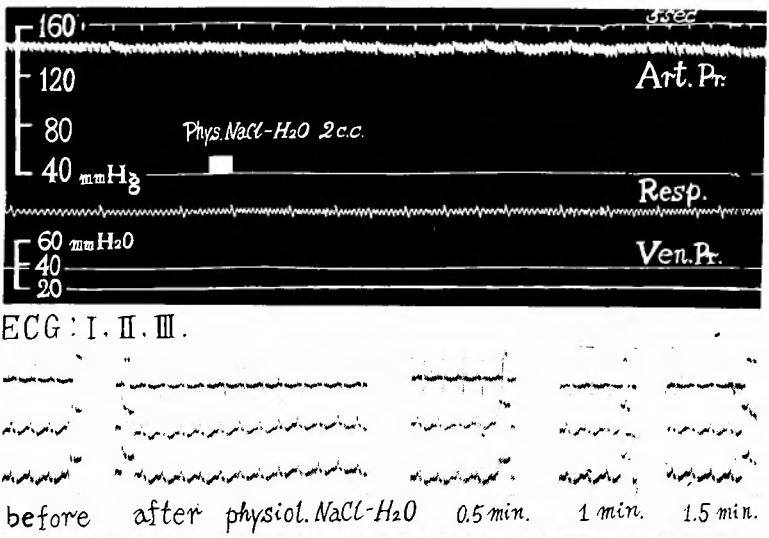


Fig. 4. Injection of isotonic saline solution into the normal pericardium.

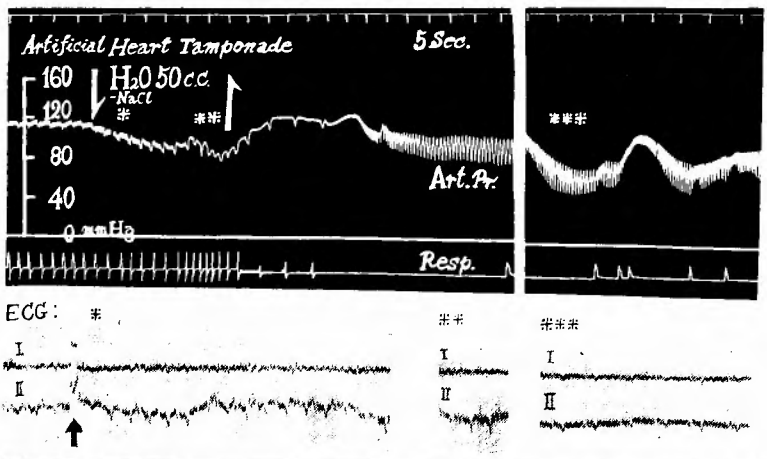


Fig. 5. Injection of isotonic saline solution into the normal pericardial cavity. (↓ shows injection of 50cc isotonic saline soluton, ↑ removal of the solution.)

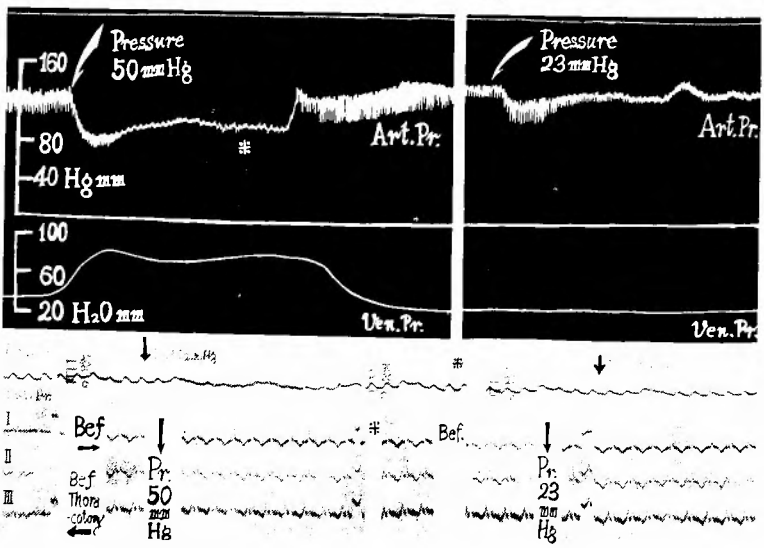


Fig. 6. Injection of air into the rubber bag fixed in the normal pericardial cavity. (↓ shows injection of the air into the bag.)

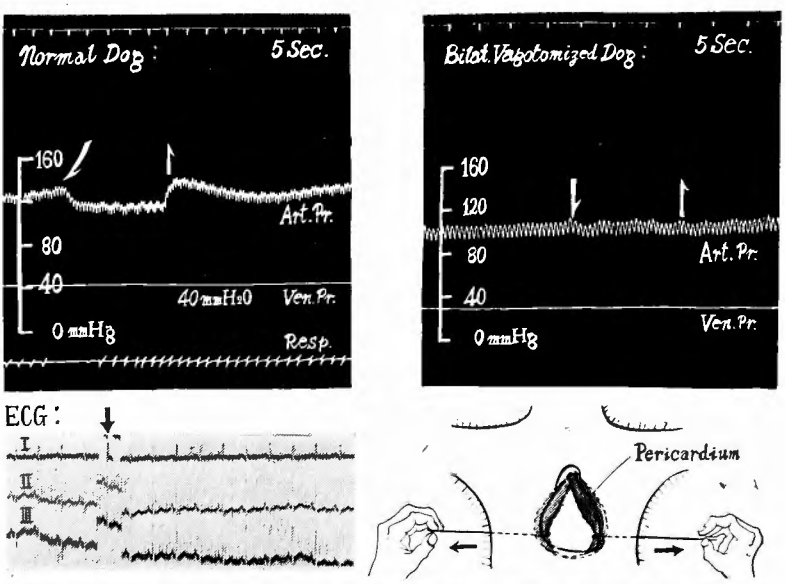


Fig. 7. Selective stretching of the normal pericardium. (↓ shows the stretching, ↑ the relaxation.)

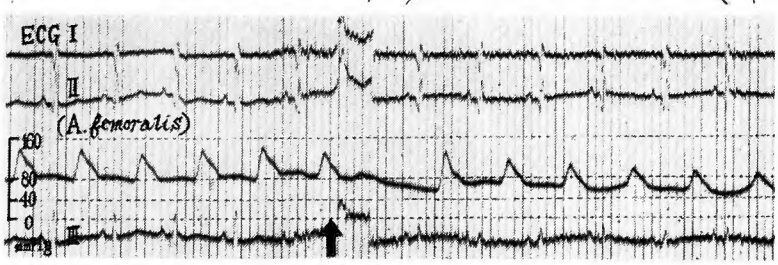


Fig. 8. Selective stretching of the normal pericardium. (By electromanometer; ↑ shows the stretching, ↓ the relaxation.)

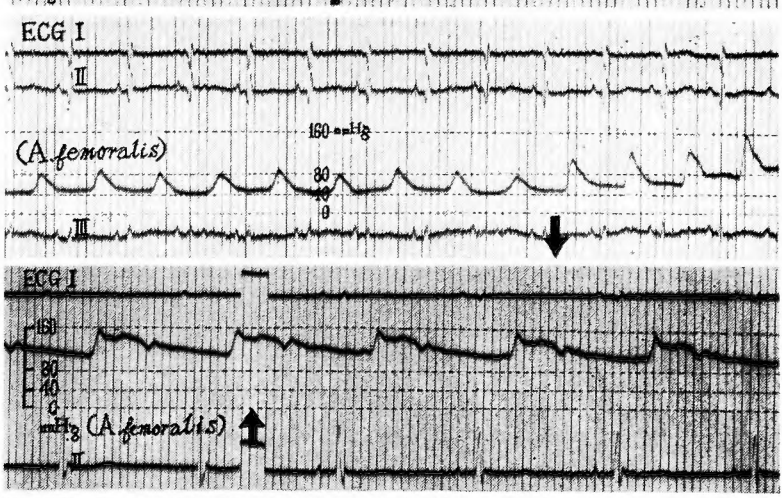
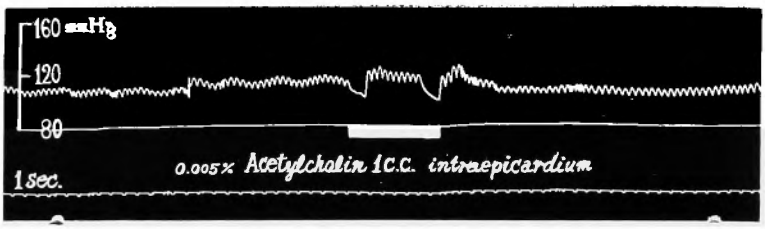


Fig. 9. Selective stretching of the pericardium with bilateral cervical section of the vagi. (By electromanometer; ↑ shows the stretching, ↓ the relaxation.)

Fig. 10.
(a) Subepicardial injection of acetylcholine.

(a)



(b) Intrapericardial injection of epirenamine hydrochloride.

(b)

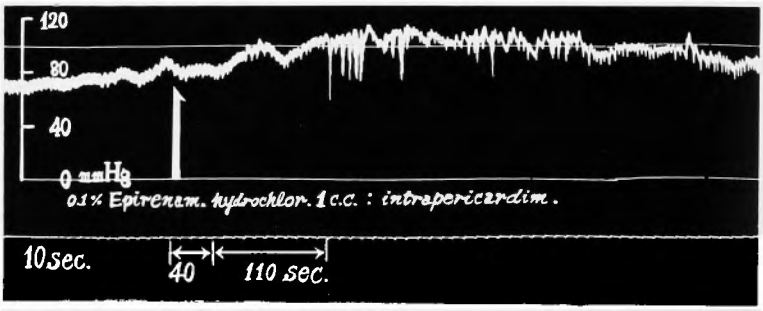


Fig. 12. Injection of acetylcholine into the normal pericardial cavity.

(a) Iniection of acetylcholine

(a)

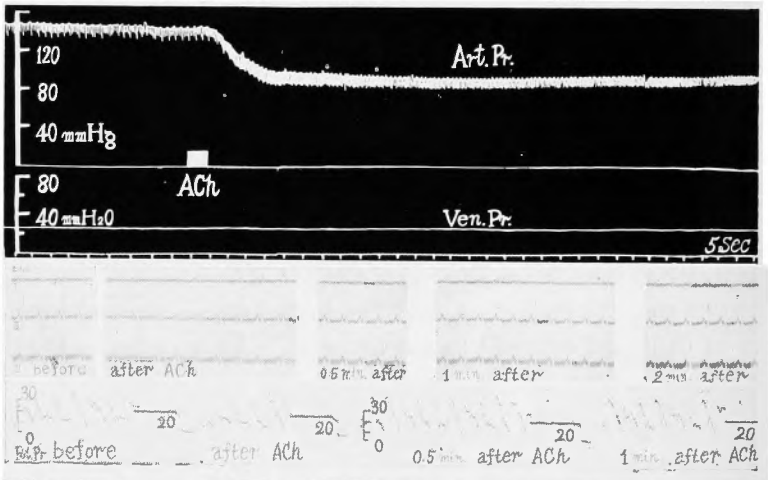
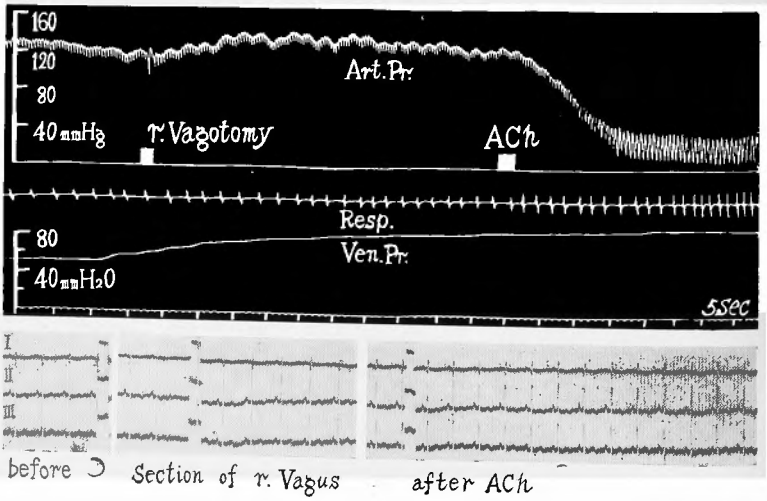


Fig. 13. Injection of acetylcholine into the pericardial cavity in the case of unilateral cervical section of the vagus.

(a) right unilateral cervical section of the vagus.

(a)



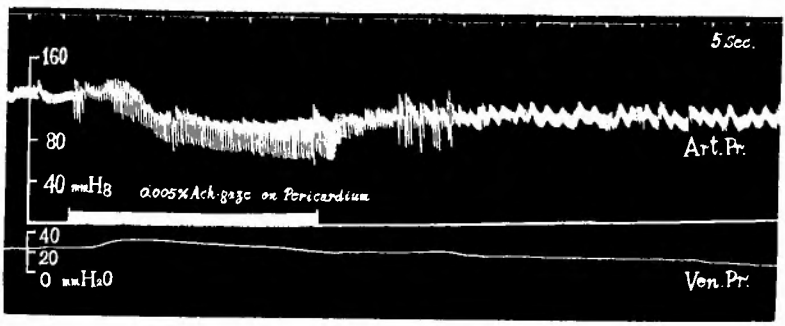
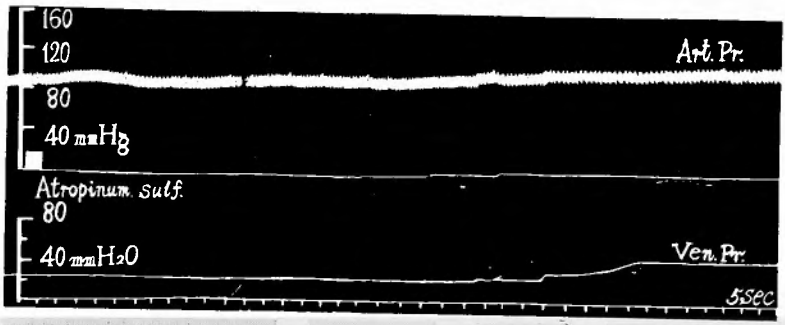
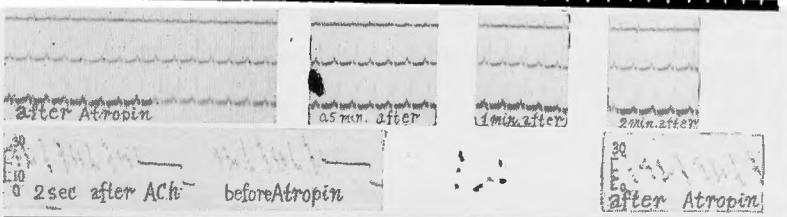


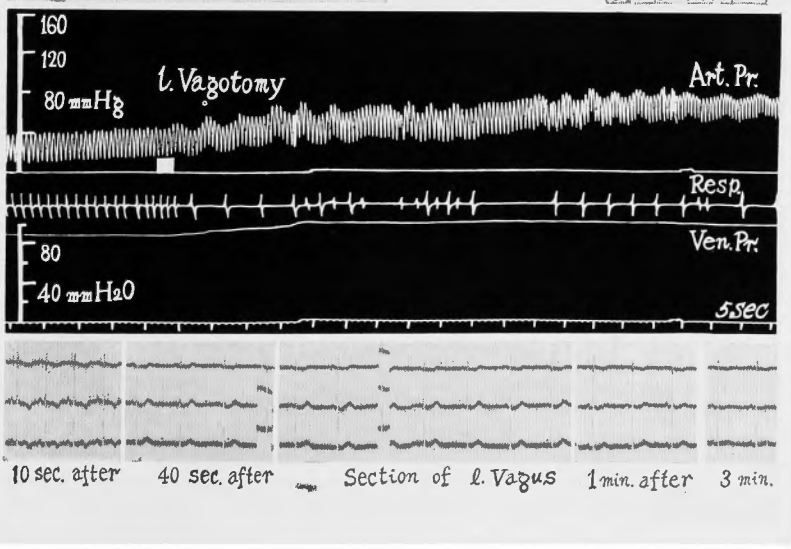
Fig. 11. Stimulation with acetylcholine of the inside of the normal pericardium.



(b) Injection of atropine.



(b)



(b) Left cervical branch of the vagus was also severed 2 minute later.

(b)

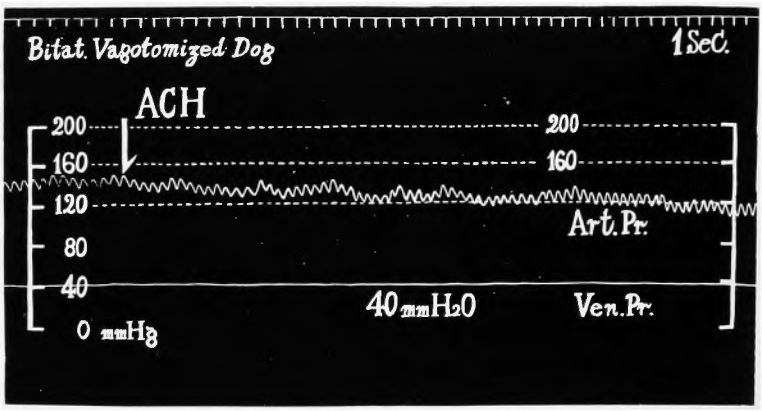


Fig. 14. Injection of acetylcholine into the pericardial cavity in the case of bilateral cervical section of the vagi.

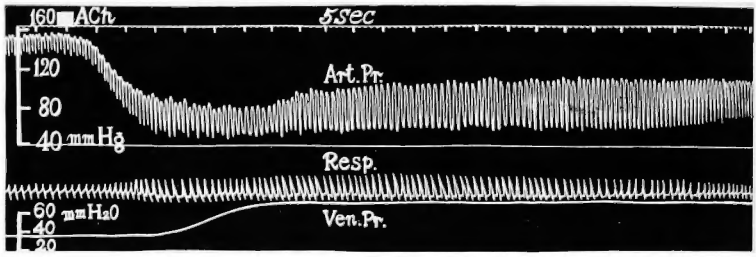
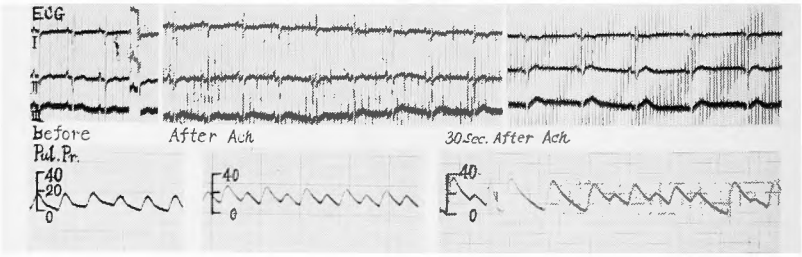


Fig. 16. Stimulation with acetylcholine of the partially adherent pericardium. (10 Days after operation.)



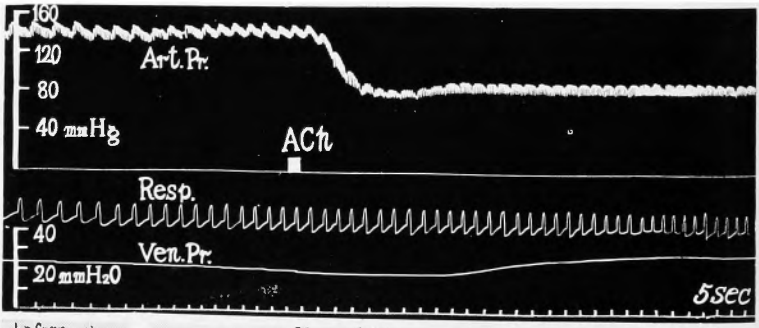
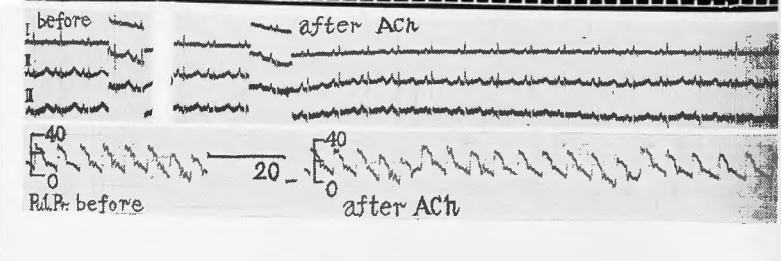


Fig. 17. Stimulation of the wholly adherent pericardium with acetylcholine. (1 Month after operation.)



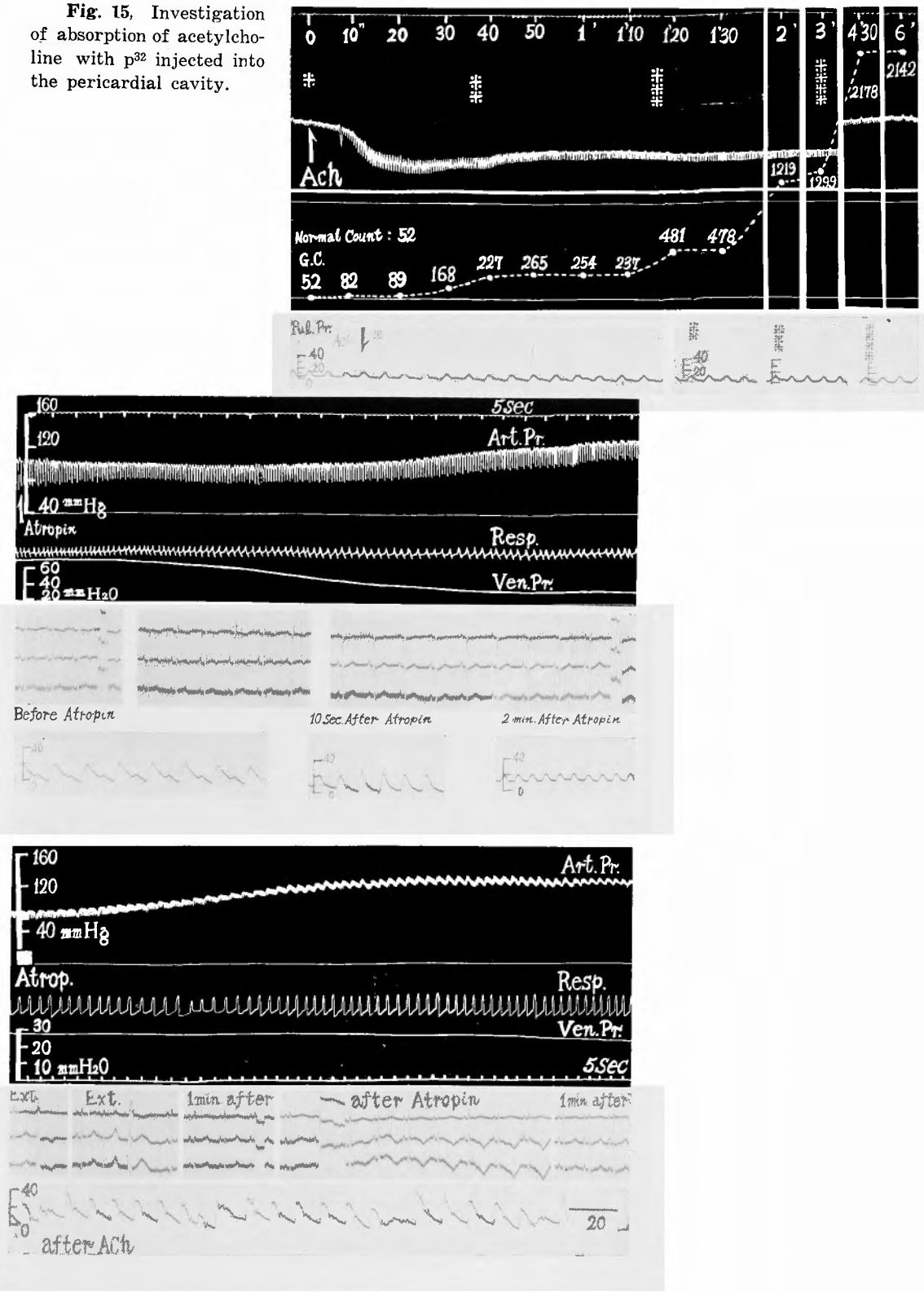


Fig. 15. Investigation of absorption of acetylcholine with p^{32} injected into the pericardial cavity.

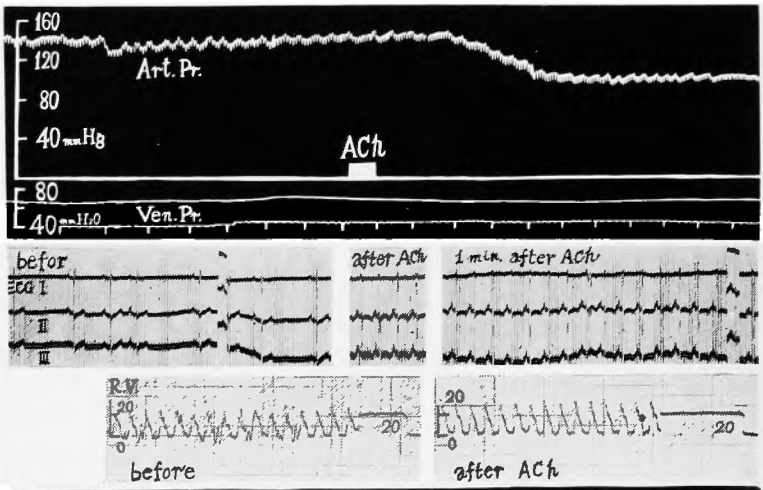


Fig. 18. Stimulation of the constrictive adherent pericardium with acetylcholine. (2 Months after operation.)

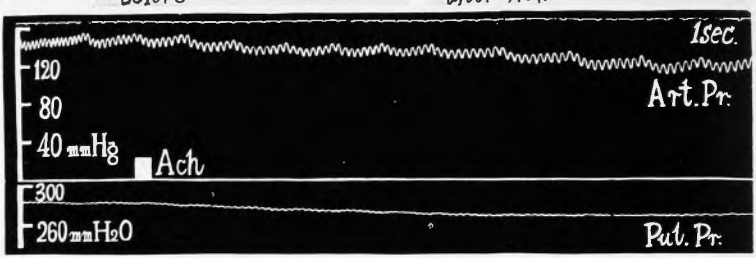


Fig. 19. Effects of stimulation with acetylcholine on long-standing pericardial adhesion. (16 Months after opration.)

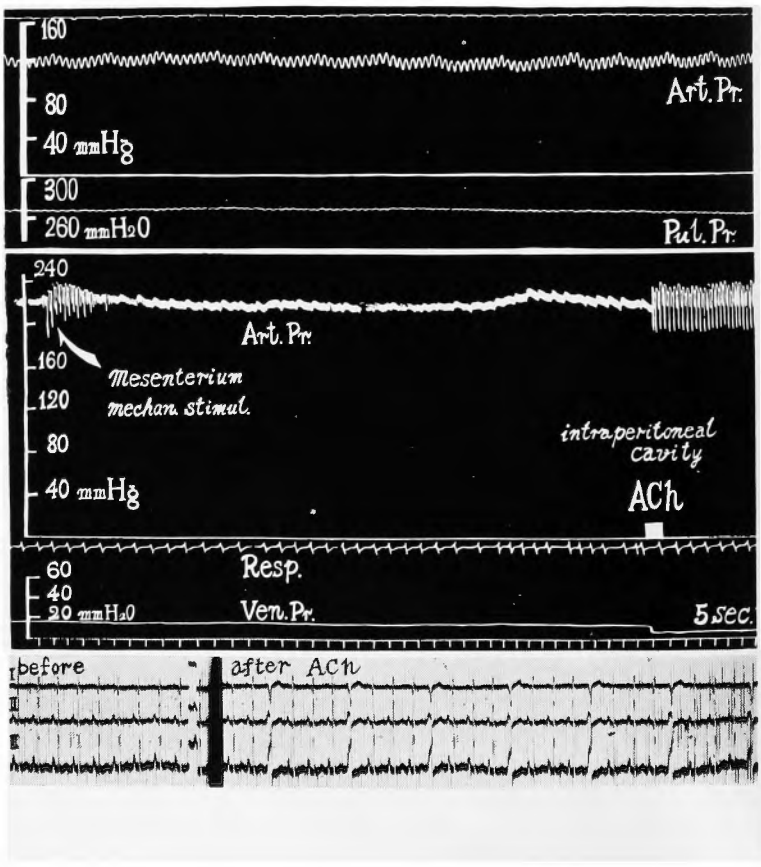
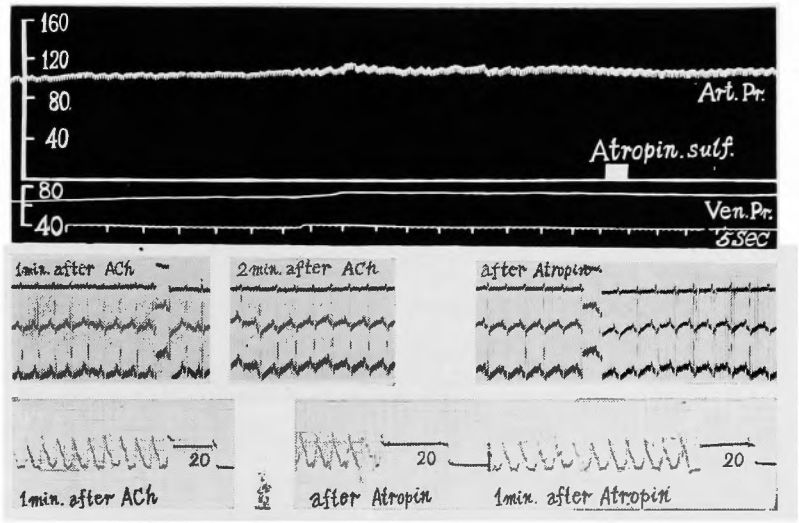
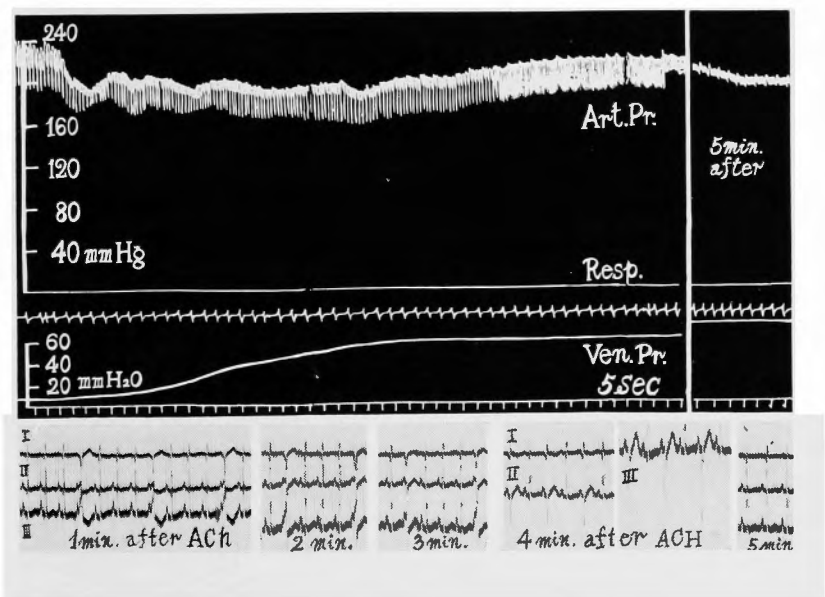


Fig. 20. Injection of acetylcholine into the normal peritoneal cavity.


160
120
80
40
Art. Pr.
Atropin. sulf.
80
40
Ven. Pr.
5 sec
1 min. after ACh
2 min. after ACh
after Atropin
20
1 min. after ACh
after Atropin
1 min. after Atropin


240
160
120
80
40 mm Hg
Art. Pr.
Resp.
5 min. after
60
40
20 mm H2O
Ven. Pr.
5 sec
I
II
III
1 min. after ACh
2 min.
3 min.
4 min. after ACH
5 min.

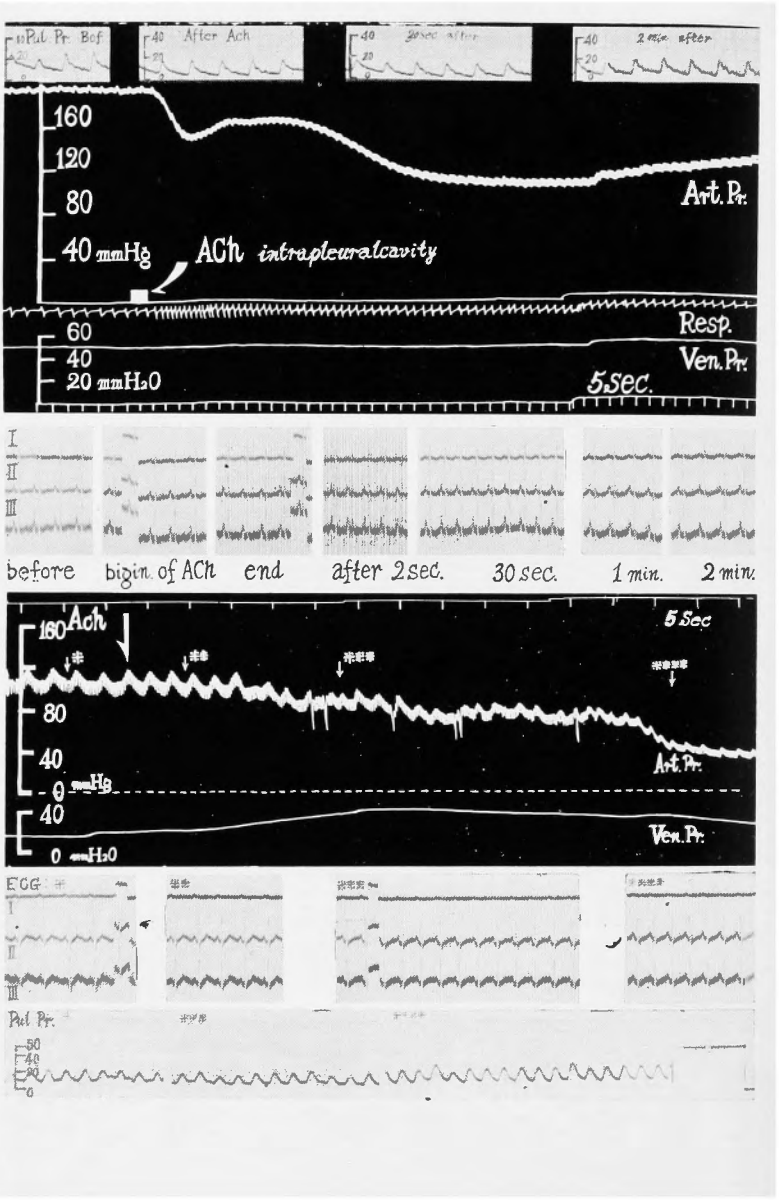


Fig. 21. Injection of acetylcholine into the normal pleural cavity.

Fig. 22. Injection of acetylcholine into the adherent pleural cavity.